Role of Oxidative Stress in Psoriasis: An Evaluation Study

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Abstract: Background: The etiopathogenesis of psoriasis has not been elucidated. Oxidative stress resulting from oxidant/antioxidant imbalance may play a role. The aim of this study was to evaluate the possible role of oxidative stress in the pathogenesis of psoriasis. The effect of antioxidant therapy was also studied in some psoriatic patients. **Methods:** Thirty four patients with chronic plaque psoriasis and 30 age and sex matched control subjects were recruited for this study. Severity of psoriasis was determined by Psoriasis Area Severity Index (PASI) score. Levels of plasma malondialhyde (MDA), catalase (CAT) and erythrocyte superoxide dismutase (SOD) were measured in patients and controls. Seven patients were given antioxidant therapy for 4 weeks. **Results**: Statistically significant higher levels of plasma MDA and CAT were detected in patients when compared with control subjects. No significant correlations with severity of psoriasis were found. Levels of MDA were positively correlated with levels of CAT in psoriatic patients. Erythrocyte SOD levels were significantly lower in patients than in controls and negatively correlated with severity of the disease but insignificantly correlated with levels of MDA in psoriatic patients. We observed no changes in PASI score, levels of MDA, CAT and SOD before and after antioxidant therapy. **Conclusion**: It is questionable whether the observed abnormalities are responsible for the onset of psoriasis, or resultant from ongoing pathologic process. Therefore, the hypothesis of an imbalance between oxidants and antioxidants in psoriasis and its role in the pathogenesis of the disease should be further investigated.
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1. Introduction

Oxidative stress may be defined as an imbalance between cellular production of reactive oxygen species (ROS) and antioxidant defense mechanisms (Lykkesfeldt, 2007). There is compelling evidence that ROS-mediated oxidative stress is involved in a vast number of biological responses causing DNA modification, lipid peroxidation, and production of inflammatory cytokines which could contribute to the pathogenesis of many inflammatory skin diseases, including psoriasis (Rashmi *et al.,* 2007).

Malondialdehyde (MDA) is the principal and most studied product of polyunsaturated fatty acid peroxidation. MDA is able to impair several physiological mechanisms of the human body through its ability to react with molecules such as DNA and proteins (Karpouzis *et al.,* 2009).

The antioxidant enzyme family of superoxide dismutases (SODs) is considered to be the first line of defense against oxygen toxicity. These metalloenzymes act to dismute toxic superoxide radicals to oxygen and hydrogen peroxide (Attwa and Swelam, 2011).

Catalase(CAT) is a tetrameric enzyme that is expressed in all major body organs. The major role of CAT as an antioxidant is its ability to detoxify hydrogen peroxide to water. Matched activities of CAT and SOD are necessary for the effective neutralization of superoxide anions and hydrogen peroxide (Nishikawa *et al.,* 2009)**.**

The aim of the present study was to evaluate the possible role of oxidant/anti-oxidant system in the pathogenesis of psoriasis through determination of the levels of plasma MDA (representing oxidant activity), plasma CAT and erythrocyte SOD (representing antioxidant activities) in psoriatic patients and their relations to the severity of the disease. We also studied the effect of antioxidant therapy on some patients.

2. Subjects And Methods

The study was carried out in Dermatology and Venereology and Clinical Pathology departments at Zagazig University Hospitals from January 2011 to December 2011.

The selection criteria and protocol were approved by the local Institutional Review Board (IRB) and all subjects signed an informed consent.

The study included 34 patients with chronic plaque psoriasis (22 males and 12 females) with mean age 42.9 ±15.7 and 30 age-and sex- matched healthy subjects as a control group (16 males and 14 females) with mean age 42.6±13.9. Patients were diagnosed clinically and when required

histopathologically. Duration of psoriasis ranged between 2months and 30 years.

Exclusion criteria included conditions that could affect the redox state such as obesity, smoking and diseases such as diabetes mellitus, cardiovascular diseases, liver or kidney diseases and inflammatory skin diseases. Psoriatic patients with any topical therapy or systemic antioxidant therapy within 4 weeks or systemic drug therapy or photochemotherapy within 3months were excluded from the study.

Clinical severity of psoriasis was determined according to the Psoriasis Area Severity Index (PASI) score. According to PASI score patients were classified into 3 subgroups:

1. Mild group: 22 patients with PASI score less than 15.
2. Moderate group: 3 patients with PASI score between 15 and 25.
3. Severe group: 9 patients with PASI score more than 25.

Eleven psoriatic patients with different severities were given antioxidant therapy in the form of once daily tablet containing selenium 100µg, vitamin A 1500 IU, vitamin C 90mg and vitamin E 30mg for 4 weeks. PASI score, plasma MDA and CAT and erythrocyte SOD were measured before therapy (day 0) and after therapy (day 28). Seven patients only completed the study.

Laboratory investigations

Sample preparation:

Under all aseptic precautions 3 ml fasting blood sample was collected using heparinized tubes, centrifuged and plasma was separated and stored at -80 ^{0}C for levels of MDA and CAT assay. For determination of SOD, 2 ml whole blood was collected on EDETA tubes centrifuged and erythrocytes washed four times with saline, hemolysed with a nine fold volume of cold distilled water, then left to stand at 4 ^{0}C for 15 min and stored at -80 ^{o}C till assay.

Methods:

1. Colorimetric determination of MDA in plasma by method of Ohkawa *et al.* (1979).
2. Colorimetric determination of erythrocyte SOD by method of Nishikimi *et al.* (1972).
3. Colorimetric determination of plasma CAT by method of Aebi (1984).

Statistical analysis:

Data were checked, entered and analyzed by using **(SPSS version 15)** software computer package. Data were expressed as mean ± standard deviation (SD) for quantitative variables, number and percentage for categorical variables. For comparison of two means **(t test)** and (ANOVA "F") test were used for several means. Chi-square (χ^2) or fisher exact test were used when appropriate, (P<0.05) was considered statistically significant

3. Results

Plasma MDA and CAT levels showed highly significant increase in psoriatic patients compared to control subjects (P <0.001). On the other hand, erythrocyte SOD levels showed highly significant decrease in psoriatic patients compared to control subjects (P <0.001) (Table 1).

As regard correlations with severity of psoriasis, there was insignificant correlations with plasma MDA and CAT (P =0.71 and 0.11 respectively) but significant correlations with erythrocyte SOD (P <0.001). SOD levels decreased with increased severity of the disease.

However, the moderate group showed the lowest level of SOD (Table 2).

There were insignificant correlations between the duration of the disease and the levels of MDA, SOD and CAT (P > 0.05) (Table 3).

Levels of MDA showed insignificant correlation with levels of SOD but positive relation with levels of CAT in psoriatic patients (Table 4)

There was non-significant statistical difference in PASI score, MDA, CAT or SOD levels before and after treatment with antioxidant therapy (Table 5).

Table (1): Plasma MDA, CAT and erythrocyte SOD levels in patients versus controls

	Cases (n=34)	Controls (n=30)	*p*-value
MDA(range in µmol/L) Mean± SD	11-77 33.2±15.3	20-26 23.7±1,6	<0.001
CAT(range in U/L) Mean± SD	228-950 590.88±206.7	135-198 161.1±20.6	<0.001
SOD(range in U/mL) Mean± SD	(11-70.3) 42.4±13.7	(93-134) 110.8±14.0	<0.001

Table (2): Correlations of Plasma MDA, CAT and erythrocyte SOD levels with severity of psoriasis.

	Mild psoriasis (n=22)	Moderate psoriasis (n=3)	Severe psoriasis (n=9)	*P*-value
MDA range Mean± SD	11-77 34.9±18.6	23-41 30.3±9.5	22-38 30.2±5.7	0.71
CAT range Mean± SD	364-950 641±214.2	228-528 418±165.7	370-740 525±161.6	0.11
SOD range Mean± SD	28.3-70.3 47.6±9.6	16-20.3 17.7±2.3	11-55 38.1±14.4	0.001

Table (3): Correlations between the duration of psoriasis and the levels of MDA, SOD and CAT in psoriatic patients.

Parameter	r	*P*	significance
MDA	0.2	>0.05	NS
SOD	-0.19	>0.05	NS
CAT	-0.23	>0.05	NS

NS: non-significant

Table (4): Correlations between plasma MDA levels and erythrocyte SOD and plasma CAT levels in psoriatic patients

Parameter	r	*P*	Significance
MDA with SOD	0.06	>0.05	Non-significant
MDA with CAT	0.36	<0.05	Significant

Table (5): Non-significant changes in PASI score, plasma CAT, MDA and SOD levels after antioxidant therapy.

Patients on treatment(n=7)	Before treatment (Day 0)	After treatment (Day 28)	*P*
PASI	16.6 ± 17.0 5.2 – 48.2	11.83 ± 10.4 2.4 – 27.1	0.21
CAT	612.6 ± 220.6 400 – 928	690.1 ± 279.5 360 – 935	0.62
MDA	42.1 ± 22.8 20 - 77	39.7 ± 20.2 20 - 70	0.83
SOD	43.8 ± 6.4 31.8 – 50	42.0 ± 20.7 16.8 – 80.6	0.82

4. Discussion

Although there have been extensive studies on the roles of serum lipids, oxidants and antioxidants levels in psoriasis, their importance in the etiology or in the enhancement of the disease remains controversial (Jyothi *et al.,* 2011). It has been suggested that ROS may play a role in the pathogenesis of psoriasis. Generation of ROS from neutrophils, keratinocytes and fibroblasts can contribute to neutrophil activation which may play an important role in psoriatic process. ROS can act as second messengers in the induction of several biological responses such as the activation of NF-kB or AP-1, the generation of cytokines, the modulation of signaling pathways and the activation of peroxisome proliferator-activated receptors (Pourtgal *et al.,* 2007 ; Zhou *et al.,* 2009).

In the present work, we studied the possible role of oxidative stress in the pathogenesis of psoriasis through determination of plasma MDA (as an oxidant and one of the main product of lipid peroxidation), erythrocyte SOD and plasma CAT (representing antioxidant activity) and their correlations with disease severity as expressed by PASI score in 34 patients with chronic plaque psoriasis and age and sex matched 30 healthy individuals. The effect of antioxidant therapy on PASI score, levels of MDA, SOD and CAT was also studied in 7 patients.

As previously reported (Pujari *et al.,* 2010; Attwa and Swelam, 2011), we observed a significant increase in the levels of plasma MDA and decreased

levels of erythrocyte SOD in psoriatic patients compared to control subjects. These results means a creation of a condition known as oxidative stress, which indicates lipid peroxidation. This may lead to cell damage by continous chain reactions. In addition, it may be responsible for activation of phospholipase A_2, production of many mediators by arachidonate, deactivation of adenyl cyclase and activation guanilate cyclase leading to decrease in the cAMP/cGMP ratio responsible for epidermal proliferation (Popov and Lewin, 1991).

Although we did not find a correlation between levels of MDA and severity of psoriasis, some previous studies (1; Pereira *et al.,* 2004; Attwa and Swelam, 2011and Jyothi *et al.,* 2011) had reported a positive correlation between the levels of MDA and the disease severity. They suggested that their results might support the proposal that serum MDA level could be helpful in predicting the prognosis of psoriasis and add further support for the involvement of oxidative stress in the pathogenesis of psoriasis.

The significant decrease in the levels of erythrocytes SOD may be a reflection of oxidative stress caused by consumption of SOD in the process of detoxification of superoxide radicals (Pujari *et al.,* 2010). In accordance with our results, several studies had reported suppressed SOD activity in erythrocytes (Utas *et al.,* 2002; Yildirim *et al.,* 2003); neutrophils (Dogan *et al.,* 1989), tissue (Utas *et al.,* 2002) and plasma (Kural *et al.,* 2003).

A highly significant negative correlation between levels of SOD and severity of psoriasis as expressed by PASI score was noticed. The mean levels of SOD were observed to be significantly decreased from mild to severe group. However, the lowest levels were observed in the moderate group which could be attributed to the small number of the patients in it (only 3patients).

In contrast to our results, some previous studies (Thereond *et al.,* 1996; Gavan *et al.,* 1997; Utas *et al.,* 2002; Baz *et al.,* 2003) showed higher plasma SOD activity in psoriatic patients than controls which was not correlated with disease severity as expressed by the PASI score. They explained this by increased superoxide anion production during the psoriatic process in the skin as well as peripheral neutrophils. Therefore, increased SOD activity will act as a defensive mechanism that prevents oxidative damage of structural lipids and proteins important for barrier integrity.

On the other hand, plasma catalase which is another antioxidant enzyme showed significantly higher levels in psoriatic patients than control subjects but its levels did not correlate with disease severity. These high levels of plasma CAT indicate oxidative damage and are likely to be high as a compensatory mechanism to insufficiency in the antioxidant system. Similar results were reported by Polkanov *et al.* (1987) and Yildirim *et al.* (2003). However, other studies reported either decrease (Pereira *et al.*, 2004; Pujari *et al.*, 2010) or no difference (Thereond *et al.*, 1996) in CAT activity in psoriatic patients compared to healthy controls.

We found neither change in the clinical severity of psoriasis (PASI) score or in the levels of MDA, SOD and CAT before and after antioxidant therapy. However, the small number of patients (7 patients) may explain these negative results. Longer duration of antioxidans, use of other types of antioxidants in larger number of psoriasis patients might have explored a better potential therapeutic efficacy of antioxidants in psoriasis therapy.

In the report of kharaevea *et al.* (2009), 58 patients with erythrodermic psoriasis and psoriatic arthropathy showed significant clinical improvement and reduction of oxidative stress after 5 weeks treatment with conventional therapy plus supplementation with antioxidant therapy in the form of coenzyme Q_{10}, vitamin E and selenium. These different results could be explained by the concomitant use of conventional therapy, the different clinical varieties of psoriasis, the large number of patients and the higher doses of antioxidant therapy given in this study.

Although being far from conclusive, the increased plasma MDA levels and the decreased erythrocyte SOD levels in psoriatic patients could provide some evidence for a potential role of oxidative stress in the pathogenesis of psoriasis. On the other hand, the insignificant correlations between plasma MDA and CAT levels and the clinical severity of psoriasis, the increased plasma catalase levels in psoriatic patients and the absence of clinical improvement or laboratory changes after antioxidant therapy might be against the concept about the role of oxidative stress in the pathogenesis of psoriasis.

In conclusion, it is questionable whether the observed abnormalities are responsible for the onset of psoriasis, or resultant from ongoing pathologic process. Therefore, the hypothesis of an imbalance between oxidants and antioxidants in psoriasis and its role in the pathogenesis of the disease should be further investigated.

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